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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,548	06/26/2006	Stuart M. Pitson	650063.404USPC	4661

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,548	PITSON ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *14-22 and 39-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,23-38 and 48-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of species of hypertension as the disease (claim 13) and antagonist to the sphingosine kinase expression product (claim 23) in the response to restriction requirement and preliminary amendment filed July 6, 2009 is acknowledged. In the preliminary amendment, claims 7, 20-23, 32 and 45-48 have been amended. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 14-22 and 39-47 are directed to non-elected species and are withdrawn from consideration. Therefore, claims 1-13, 23-38 and 48-52 are examined.

Informalities

The disclosure is objected to because of the following informalities:

2. In the brief description of Figure 1, a term "L83RhoA" is cited, however, Figure 1 indicates it is "L63RhoA". Appropriate clarification is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 27-38 and 48-51 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-13, 23-38 and 48-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating mammalian smooth muscle cell activity by modulating the functional activity of sphingosine kinase mediated signaling in vitro, the method comprising contacting vascular smooth muscle cells with a specific sphingosine kinase such as Sphk1 (active) or hSK-G82D (inactive mutant), or a method of modulating human airway smooth muscle cell functions by sphingosine 1-phosphate as indicated in the prior art, does not reasonably provide enablement for a method of modulating or regulating mammalian smooth muscle cell activity in vivo or a method for the treatment and/or prophylaxis of a condition characterized by aberrant, unwanted or inappropriate smooth muscle cell activity in mammal, the method comprising modulating the functional activity of sphingosine kinase mediated signaling, wherein upregulating sphingosine kinase mediated signaling to a functionally effective level upregulates the smooth muscle cell activity and downregulating sphingosine kinase mediated signaling to a functionally ineffective level downregulates the smooth muscle cell activity; and a pharmaceutical composition comprising a modulating agent, where the modulating agent is not identified either in the method or the composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-13, 23-38 and 48-52 are drawn to a method of modulating or regulating mammalian smooth muscle cell activity, or a method for the treatment and/or prophylaxis of a condition characterized by aberrant, unwanted or inappropriate smooth muscle cell activity in mammal, the method comprising modulating the functional activity of sphingosine kinase mediated signaling; and a pharmaceutical composition comprising a modulating agent. The specification, however, only discloses cursory conclusions without data supporting the findings, which states that the present invention provides compositions or methods for modeling smooth muscle cell activity or for the treatment and/or prophylaxis of a condition characterized by aberrant, unwanted or inappropriate smooth muscle cell activity in mammal, the method comprising modulating the functional activity of sphingosine kinase mediated signaling (pages 4-8). The present application does not provide sufficient teachings on the use and effects of various modulating agents in the claimed methods to enable the full scope of the claims. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the modulating agents and their effects in modulating mammalian smooth muscle cell activity in vivo, or a method for the treatment and/or prophylaxis of a condition related to unwanted or

inappropriate smooth muscle cell activity, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

While the specification discloses a specific sphingosine kinase (either active Sphk1 or inactive hSK-G82D mutant) modulates microvascular tone and myogenic responses via activation of RhoA/Rho kinase (Example 1), the specification has not shown any example illustrating the use and effects of various modulating agents for in vivo treatment.

(3). The state of the prior art and relative skill of those in the art:

While the prior art (e.g., Ammit *et al.* (FASEB J. 15, 1212-1214 (2001), see below) discloses sphingosine 1-phophate (SPP) modulates human airway smooth muscle (ASM) contraction, cell growth and proinflammatory cytokine production that promote bronchoconstriction, airway inflammation and remodeling in asthma, the general knowledge and level of the skill in the art do not supplement the omitted description (i.e., the use and effects of various modulating agents for in vivo treatment). Besides the known Sphk1, hSK-G82D mutant, or SPP, a skilled artisan cannot readily identify a modulating agent that is effective in the method of treatment without further experimentation.

(4). Predictability or unpredictability of the art:

While the specification discloses sphingosine kinase (e.g., Sphk1 or hSK-G82D mutant) can modulates microvascular tone and myogenic responses, the specification does not describe the use and effect of various modulating agents for in vivo treatment. Since the specification has not shown the correlation between in vitro effect and in vivo treatment, the identities of modulating agents that are effective in the in vivo treatment are unpredictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of modulating or regulating mammalian smooth muscle cell activity, or a method for the treatment and/or prophylaxis of a condition due to unwanted or inappropriate smooth muscle cell activity in mammal, the method comprising modulating the functional activity of sphingosine kinase mediated signaling; and a pharmaceutical composition comprising a modulating agent. The specification merely discloses the use of a specific sphingosine kinase (e.g., Sphk1 or hSK-G82D mutant) to modulate microvascular tone and myogenic responses via activation of RhoA/Rho kinase (Example 1), the specification has not identified any modulating agent that is effective for in vivo treatment, nor has described the correlation between the in vitro effect and in vivo treatment. Since the specification has not shown the use and effects of various modulating agents for in vivo treatment, it is necessary to carry out undue experimentation to identify an active modulating agent and to assess its effect in the claimed method.

(6). Nature of the Invention

The scope of the claims encompasses a method of modulating mammalian smooth muscle activity using an agent that modulates the functional activity of sphingosine kinase mediated signaling, but the specification does not provide sufficient information regarding the identity of the modulating agent that is active for the in vivo treatment. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed methods associated with variants, the structure of the active modulating agent is

unpredictable, and the teachings in the specification are limited, therefore, it is necessary to carry out undue experimentation to identify active modulating agents and to assess their in vivo effects in the claimed methods.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-13, 23-38 and 48-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 27-38 and 48-51 provide for the use of an agent capable of modulating the functionally effective level of sphingosine kinase mediated signaling in the manufacture of a medicament, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass.. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

7. Claims 1-13 and 25-26 are indefinite because the claim recites modulating the functional activity of sphingosine kinase mediated signaling without indicating an active step, thus, it is not clear how the modulating the functional activity of sphingosine kinase mediated signaling is carried out. Claims 4-13 and 25-26 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

8. Claims 1-13 and 23-26 are indefinite because the claims lack an essential step in the process of modulating smooth muscle cell activity or treating a condition. The missing step is an

effective amount of modulating agent administered. Claims 4-13 and 23-26 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

9. Claim 52 is indefinite because of the use of the term "the modulatory agent as hereinbefore defined". The term cited renders the claim indefinite, it is not clear what is the modulatory agent which is not defined in the claim.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-4, 7, 25-26, 28, 29, 32 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as unpatentable over Ammit *et al.* (FASEB J. 15, 1212-1214 (2001)).

Ammit *et al.* teach Sphingosine 1-phophate (SPP) modulates human airway smooth muscle (ASM) contraction, cell growth and proinflammatory cytokine production (Fig. 2) that promote bronchoconstriction, airway inflammation and remodeling in asthma, and SPP levels

were elevated in the airways of asthmatic (but not control) subjects after segmental antigen challenge (Fig. 1; pages 1212-1214; claims 1-4, 7, 25-26, 28, 29, 32). Although Ammit *et al.* do not specifically teach a pharmaceutical composition comprising SPP and one or more pharmaceutically acceptable carriers, it is obvious that a pharmaceutical composition comprising SPP and one or more pharmaceutically acceptable carriers (e.g., water) was prepared (claim 52) since SPP composition is used to treat human ASM cells for monitoring IL-6 secretion (Fig. 2; page 1213).

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Chih-Min Kam/
Primary Examiner, Art Unit 1656

CMK

September 10, 2009